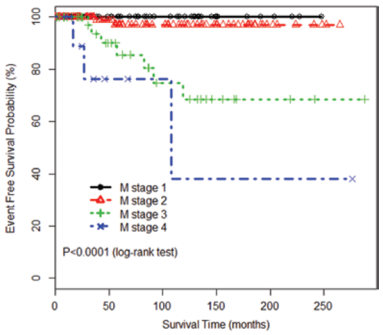
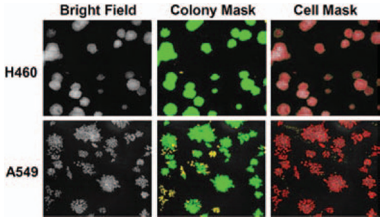
IN THIS ISSUE

- **Prognostic Factors for Cure, Recurrence, and Long-Term Survival After Surgical Resection of Thymoma**



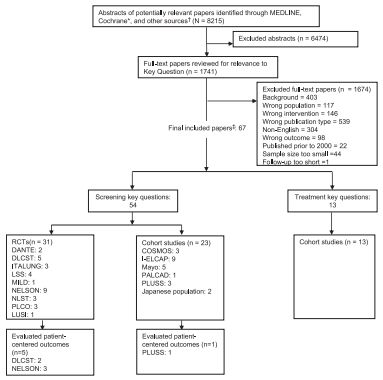
This study was a retrospective analysis of a large cohort of thymoma patients to evaluate the association between survival and WHO histology, tumor size, Masaoka stage, and completeness of resection. Thymic resection was performed at Toronto General Hospital (1986–2010) where radiotherapy has generally been recommended in all incomplete resections and stage 2b or greater tumors. Histology of many cases (200 of 262) was analyzed by the WHO classification. Patients were followed up every 6 months for the first 2 years and then annually with computed tomography of the thorax. Eighty three percent of patients had complete resection. Overall survival was 95% at 5 years, 91% at 10 years, and 91% at 15 years. Twelve patients had recurrence, of which three were local mediastinal recurrences. Univariate analysis demonstrated that increased Masaoka stage, incomplete resection, larger tumor size, and increased age were significantly associated with increased recurrence ($p < 0.0001$, $p < 0.0009$, $p < 0.0002$, and $p < 0.04$, respectively). Multivariate analysis showed that only increased Masaoka stage and tumor size (> 7.0 cm, as a continuous predictor) were associated with increased recurrence ($p < 0.0001$ and $p < 0.03$, respectively). Gender, WHO histology, and adjuvant radiotherapy were not significant predictors of recurrence. To conclude, the findings from this study of 262 cases demonstrated incomplete resection, tumor size greater than 7 cm, and higher Masaoka stage as adverse prognostic factors. The long-term survival data also supported complete surgical resection to improve long-term cure. The roles of neo-adjuvant or adjuvant chemotherapy and/or radiotherapy in improving the outcome of stage III and IV tumors with recurrence should also be explored. (p. 1018)

- **A High Content Clonogenic Survival Drug Screen Identifies Mek Inhibitors as Potent Radiation Sensitizers for Kras Mutant Non–Small-Cell Lung Cancer**



This article described the application of a novel method, high content clonogenic survival assay, developed by Lin et al. for the identification of potential radiation sensitizers from screening drug libraries. Cells in 96-well plates were subject to drug treatment, irradiation, and incubation, followed by colony staining with crystal violet, imaging, and analysis on the INCell 6000 (GE Health). H460 lung cancer cell line (KRAS mutant) and a Custom Clinical Collection (146 compounds) were used in a proof-of-principle screen. The findings revealed that a few drugs of the same class sensitized cells to radiation with clinically relevant potency. Enhanced effects of radiation in H460 cells were observed with inhibitors of PI3K, AKT, mTOR, and MEK1/2 downstream of KRAS, particularly there were synergistic effects of tramenitib (MEK1/2 inhibitor) in KRAS mutant but not wild-type lung cancer cells. The authors concluded that high content clonogenic survival assay facilitates drug screening for novel radiation sensitizers, which would in turn speed up their discovery and development into clinical studies. (p. 965)

- **Patient-Centered Outcomes among Lung Cancer Screening Recipients with Computed Tomography: A Systematic Review**



The authors reviewed data obtained from the Cochrane Central Registry of Controlled Trials and Cochrane Database of Systematic Reviews, MEDLINE, reference lists of papers, and Scopus to determine the impact of low-dose computed tomography (LDCT) screening and subsequent results on patients' quality of life, distress, and anxiety. Only randomized controlled trials (RCT) involving asymptomatic adults were included in the analysis of the effect of LDCT screening on patient-centered outcomes, whereas RCTs and cohort studies were included for the analysis of association of subsequent results and/or recommendations from LDCT screening with patient-centered outcomes. Of the 8215 abstracts reviewed, five publications from two European RCTs and one publication from a US cohort study were included in this analysis. The findings revealed an association between the process of LDCT screening and short-term psychologic discomfort, whereas over the long term, no significant impact was observed with distress, worry, or overall health-related quality of life. In the short term, negative results were linked to decline in distress whereas false positive results were linked to elevated distress, which reversed to levels similar to that in negative results. Taken together, this study suggested possible short-term distress as a result of false positive results from LDCT screening should be taken into consideration when individuals are going through the procedure, possibly through effective communications with clinicians to reduce the distress. (p. 927)

RESEARCH WATCH

- **Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors versus Conventional Chemotherapy in Non–Small-Cell Lung Cancer Harboring Wild-Type Epidermal Growth Factor Receptor: A Meta-Analysis**

In a meta-analysis conducted by Lee et al., eligible randomized controlled trials were reviewed to determine the association of first generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and chemotherapy with survival in advanced non–small-cell lung cancer patients harboring wild-type (WT) EGFR. Of 1947 articles from PubMed, EMBASE, Cochrane database, and meeting abstracts of the American Society of Clinical Oncology and European Society of Medical Oncology, 11 trials involving 1605 patients with WT EGFR were included. Progression-free survival (PFS) was the primary outcome, whereas objective response rate and overall survival (OS) were the secondary outcomes. Improved PFS and objective response rate were observed in the chemotherapy arm versus the TKI arm (hazard ratio for TKI 1.41; 16.8% versus 7.2%), regardless of line of treatment, experimental drug, dominant ethnicity, or EGFR mutation analysis method. However, there was no statistically significant difference in OS between the arms (hazard ratio for TKI, 1.08). The authors concluded that conventional chemotherapy was associated with improved PFS but not OS, when compared with first generation EGFR TKI in advanced non–small-cell lung cancer patients with WT EGFR.

Lee J, Hahn S, Kim D, et al. Epidermal growth factor receptor tyrosine kinase inhibitors vs conventional chemotherapy in non–small cell lung cancer harboring wild-type epidermal growth factor receptor: A meta-analysis. JAMA 2014;311:1430–1437.

- **A Randomized, Multicenter, Placebo-Controlled Clinical Trial Of Racotumomab-Alum Vaccine as Switch Maintenance Therapy In Advanced Non–Small-Cell-Lung Cancer Patients**

This clinical study investigated the efficacy and safety of racotumomab, a vaccine that targets the NeuGcGM3 tumor-associated ganglioside, as switch maintenance for stage III/IV non–small-cell lung cancer patients with prior first-line chemotherapy. The primary endpoint was overall survival (OS). The 176 patients randomized to racotumomab-alum and placebo (1:1) achieved a median OS of 8.23 and 6.80 months, respectively (hazard ratio 0.63; $p = 0.004$). The vaccinated group also had improved median progression-free survival (5.33 months) versus placebo (3.90 months;hazard ratio 0.73; $p = 0.039$). Adverse events such as burning and pain at the injection site, bone pain, and asthenia were most common in the vaccinated group. Results also showed a high antibody response against the NeuGcGM3 ganglioside and its specificity in killing ≥30% NeuGcGM3-expressing L1210 cell line. Patients who developed the antibodies had prolonged median survival. The authors concluded that racotumomab-alum as switch maintenance is effective and well-tolerated for advanced non–small-cell lung cancer patients. However, the sample size is very small and a larger confirmatory study has to be performed.

Alfonso S, Valdes-Zayas A, Santiesteban ER, et al. A randomized, multicenter, placebo-controlled clinical trial of racotumomab-alum vaccine as switch maintenance therapy in advanced non-small-cell-lung cancer patients. Clin Cancer Res, 2014. doi:10.1158/1078-0432.ccr-13-1674.

- **FGFR1 mRNA and Protein Expression, Not Gene Copy Number, Predict FGFR TKI Sensitivity Across All Lung Cancer Histologies**

Wynes et al. evaluated the use of FGFR1 mRNA and protein expression as better biomarkers of FGFR tyrosine kinase inhibitor (TKI) sensitivity in lung cancer in comparison with the use of FGFR1 gene copy number (GCN), which assumes that only increased GCN is involved in increased FGFR1 signaling. The sensitivity to ponatinib, a potent FGFR TKI, was assessed in a range of histologically different lung cancer cell lines. FGFR1 GCN and mRNA analysis were performed on a tissue microarray of resected lung tumors. Ponatinib sensitive cell lines (14 of 58) with IC50 values less than 50 nM demonstrated an association with FGFR1 mRNA and protein expression and mRNA expression of the ligands FGF2 and FGF9, but not with FGFR1 GCN or histology. High FGFR1 mRNA expression was found in 22% of adenocarcinomas and 28% of SCCs of the resected tumors, but only less than half of SCCs with high FGFR1 GCN showed high mRNA levels. The findings were validated with TCGA lung cancer data and also uncovered the overlapping FGFR1 mRNA expression with KRAS and PIK3CA mutations. To conclude, this study indicates that FGFR1 mRNA could be a better biomarker of FGFR TKI sensitivity in lung cancer of various histologies when compared with FGFR1 GCN.

Wynes MW, Hinz TK, Gao D, et al. FGFR1 mRNA and protein expression, not gene copy number, predict FGFR TKI sensitivity across all lung cancer histologies. Clin Cancer Res, 2014. doi:10.1158/1078-0432.ccr-13-3060.

- **Rapidly Increasing Promotional Expenditures For e-Cigarettes**

This Industry Watch by Kronfield et al. was aimed to analyze and track expenditures in marketing e-cigarettes. Data were obtained from Kantar Media, where information on US advertising across media platforms (television, print, radio, and the internet) and expenditure estimates from market rate (starting from 2008) were available. Keywords used in the search of data included generic terms for e-cigarettes and component parts, slang terms, and brand names. The findings revealed 132 unique brands, mostly e-cigarette brands, with advertising expenditures from the beginning of 2008 to mid-2013. Promotional spending has risen dramatically since mid-2010 to US$12 million in 2011 and US$22 million in 2012. Expenditures in the second quarter of 2013 (US$28 million) was eightfold higher than that in the same time of 2012. Many of 2013 expenditures were in print media, followed by television; more than 60% of these expenditures were for a brand called Blu. Taken together, this study showed a continued rapid rising trend in e-cigarette promotional spending and projected a further rise in television advertising along with a rise in the market share by tobacco companies. The actual extent of e-cigarette promotional spending could be underestimated in this study where internet promotion including social media and sponsored events were not covered. The authors emphasized the need for continued monitoring of e-cigarette marketing spending, and further studies on the content of e-cigarette promotional messages across media channels to guide product regulation and policy and to evaluate the claims made in the messages and their impact on consumers.

Kornfield R, Huang J, Vera L, Emery SL. Rapidly increasing promotional expenditures for e-cigarettes. Tobacco control, 2014. doi:10.1136/tobaccocontrol-2014-051580.

- **Stimulation of Soluble Guanylate Cyclase Prevents Cigarette Smoke-Induced Pulmonary Hypertension and Emphysema**

Weissmann et al. sought to determine the role of the soluble guanylate cyclase (sGC)-cGMP pathway in the pathogenesis of lung emphysema and pulmonary hypertension (PH), as well as its potential in therapeutic intervention for these diseases. A series of molecular techniques and functional tests were performed in lung tissues of healthy individuals and COPD patients, in mice and guinea pigs. Mice and guinea pigs were exposed to cigarette smoke (CS) for a period of time, followed by treatment with sGC stimulators. The results demonstrated a reduced level of sGC β1-subunit in COPD patients and CS-exposed mice. Treatment with sGC stimulators suppressed the development of PH and emphysema in CS-exposed mice and guinea pigs. The treatment also inhibited peroxynitrite-induced apoptosis of alveolar and endothelial cells, reduced CS-induced inflammatory cell infiltrate in lung parenchyma, and inhibited adhesion of CS-stimulated neutrophils. This study indicates that the sGC-cGMP pathway is disrupted in chronic CS exposure, and stimulation of this pathway could be a promising treatment for COPD that will inhibit CS-induced PH and emphysema.

Weissmann N, Lobo B, Pichl A, et al. Stimulation of soluble guanylate cyclase prevents cigarette smoke-induced pulmonary hypertension and emphysema. Am J Respir Crit Care Med, 2014. doi:10.1164/rccm.201311-2037OC.

NEWS-IN-BRIEF

- **FDA Approves Ceritinib for Metastatic Lung Cancer**

Photo source: CDC

Ceritinib (Zykadia) has been granted accelerated approval by the FDA for the treatment of patients with metastatic ALK-positive non–small-cell lung cancer (NSCLC) with prior crizotinib treatment. This approval came 4 months ahead of review completion. Zykadia, an ALK tyrosine kinase inhibitor, has shown promising results in the clinical trial of 163 ALK-positive metastatic NSCLC patients, in which about half of the patients had tumor shrinkage that lasted an average of about 7 months. Common adverse events were diarrhea, abdominal pain, nausea, and vomiting. Increased liver enzymes, pancreatic enzymes, and increased glucose levels were also reported.

- **Revolutionary Clinical Trial to Individualize Lung Cancer Treatment**

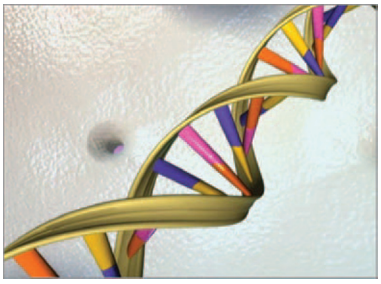


Photo source: NIH

Partnership between Cancer Research UK, AstraZeneca, Pfizer, and the National Health Service (NHS) has resulted in the opening of the "National Lung Matrix" trial later this year at centers across the United Kingdom toward personalized treatments for patients with advanced lung cancer. Researchers would have unprecedented access to drug libraries of AstraZeneca and Pfizer and are able to evaluate up to 14 medicines within one trial. With the availability of the genetic profiles of each lung tumor, researchers could stratify patients for optimal treatment outcomes. Promising drugs might be accelerated into larger trials in patients matching the same genetic profiles. New drugs could also be added to the existing trial when novel experimental treatments are available from the laboratory. This trial is led by chief investigator Gary Middleton in conjunction with the Early Drug Development Team at the Cancer Research UK Clinical Trials Unit in Birmingham and will contribute to the first phase of Cancer Research UK Stratified Medicine Program. This will also allow routine testing of patient tumor samples in NHS hospitals to match patients to the best treatment possible.

- **AATS Annual Meeting 2014: Breath Analysis Offers Noninvasive Method to Detect Early Lung Cancer**

Previous study identified carbonyl compounds found in the breath as elevated cancer markers, which could distinguish patients with benign lung disease from those with lung cancer. In this study, researchers sought to compare the sensitivity and specificity of a noninvasive tool, coated with silicon microchips for breath analysis, with PET scans in lung cancer detection. Michael Bousamra II presented the preliminary data at the 94th American Association for Thoracic Surgery annual meeting. From a group of 88 healthy controls, 107 lung cancer patients, 40 individuals with benign pulmonary disease, and seven with metastatic lung cancer, the investigators found that the sensitivity and specificity of breath analysis was dependent on the number of elevated cancer markers: 0 or 1 in most benign pulmonary disease; 3 or 4 in stage IV cancer. When used to differentiate early-stage lung cancer from benign disease, breath analysis, and PET scanning showed similar sensitivities (82.8% and 90.3%, respectively). But a much higher specificity was found in breath analysis versus PET scanning to distinguish benign disease (75% versus 38.7%, respectively), indicating higher accuracy in breath analysis to identify individuals without cancer and hence avoiding unnecessary invasive procedure. The findings suggested that this noninvasive breath analysis offers a cheaper and more reliable diagnosis for those without significant disease and rapid and accurate diagnosis in conjunction with a positive CT scan result for those with lung cancer to expedite treatment.

- **e-Cigarettes**

Photo source: FDA

This has been a big month for e-cigarette literature and news. In Australia, the Sydney Morning Herald reported on April 27 the banning of the sale of electronic cigarettes in Western Australia. The paper reports that the ban follows a WA Health Department appeal over a magistrate decision that there was insufficient evidence to suggest that e-cigarettes resembled tobacco cigarettes.

http://www.smh.com.au/national/health/electronic-cigarettes-the-truth-behind-the-smoke-and-mirrors-20140426-37aum.html . The appeal was successful; the Western Australian Supreme Court decision (April 10), among other things, concluded that e-cigarettes were "designed to resemble a tobacco product" referring "particularly [to] the conveyance of the electronic cigarette to the user's mouth using their hand, the inhalation and exhalation of the vapor, and the fact that the vapour is reminiscent of the smoke from a cigarette". www.supremecourt.wa.gov.au. NBC News reports on a study from Legacy, an American tobacco control not-for-profit organization, examining the marketing of e-cigarettes to young people, was released on May 1, 2014. The report addresses concerns that include dual use of cigarettes and e-cigarettes and therefore reduction in quitting, the potential for harm from e-cigarettes, the rise of e-cigarette use among young people and marketing strategies such as flavored e-cigarettes and high levels of advertising spending across television, print media, and online. According to the NBC report, not only is the use of e-cigarettes rising among young people, a major e-cigarette brand, Blu, is owned by a major tobacco company Lorillard which, according to a Bloomberg Business week report, attributes 4% of its revenue from e-cigarettes. In light of all this, restrictions on e-cigarettes are developing in New York State (from the New York Post) and Chicago (Chicago Tribune) as the FDA considers regulation of e-cigarettes. A proposed rule by the FDA (open for comment until the 7th of July 2014) seeks to extend the definition of "tobacco product" over which the FDA has regulatory authority to include new categories, including e-cigarettes; CNN reports a proposed age limit of 18 for purchase of e-cigarettes once the rule becomes final (http://edition.cnn.com/2014/04/24/health/fda-e-cigarette-regulations/). You can read the rule on the FDA website (link below).

http://www.nbcnews.com/health/kids-health/e-cigarette-makers-going-after-youth-report-finds-n94166.

http://legacyforhealth.org/content/download/4542/63436/version/1/file/LEG-Vaporized-E-cig_Report-May2014.pdf.

http://www.businessweek.com/articles/2013-10-23/blu-e-cigarettes-help-lorillard-capture-half-the-u-dot-s-dot-market.

http://nypost.com/2014/04/29/albany-moves-to-ban-e-cigs-in-public-after-citys-ban/.

http://www.chicagotribune.com/news/local/ct-e-cigarette-indoor-ban-met-20140430,0,565726.story.

https://www.federalregister.gov/articles/2014/04/25/2014-09491/deeming-tobacco-products-to-be-subject-to-the-federal-food-drug-and-cosmetic-act-as-amended-by-the.

- **Lung Cancer Screening in Smokers**

Photo source: FDA

Medpage Today (www.medpagetoday.com) reported on May 1 the rejection of low-dose CT screening for lung cancer by a Medicare Advisory Panel. The article reports on the surprise and disappointment of the presenting medical professionals in light of the results of the National Lung Screening Trial. The panel is not because of make final this decision until 2015 but, it is reported, no other highly powered trials are expected to be complete by then.

- **Plain Packaging—The Fight Continues**

Photo credit: Pumpmeup at en.wikipedia | CC BY-SA 3.0 US | Photo unaltered.

The effort to introduce a bill for plain cigarette packaging in New Zealand attracted some controversial comment in April when the health select committee overseeing a briefing decided to show to the media, artwork by children in support of the bill. Business Day reports that the committee will hold a briefing on more than 17,000 submissions on the Smoke-Free Environments (Tobacco Plain Packing) Amendment Bill, 10,000 of which are thought to have been arranged in a campaign run by New Zealand's major tobacco companies. The bill is expected to pass but the NZ Government has indicated that it would wait for a WTO challenge to Australia's plain packaging legislation before proceeding further.
http://www.stuff.co.nz/business/industries/9939539/Plain-pack-tobacco-fight-heats-up.

- **"Tobacco is Murderous"**

The BBC reports on a meeting between US President Barack Obama and the Uruguayan Presdent Jose Mujica where they discussed Uruguay's restrictions on tobacco smoking. Uruguay introduced a ban on smoking in public places in 2006 and is currently being sued by Philip Morris, the global tobacco company. Mr. Mujica was quoted in strong language, "eight million people die each year [in the work] from smoking tobacco....this is mass murder. We are in an arduous fight....against very strong [corporate] interests."
http://www.bbc.com/news/world-latin-america-27383896.